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SHORT REPORT



# Presence of inflammatory proteins S100A8 and S100A9 in a giant intracranial aneurysm after flow diverter treatment

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**ABSTRACT**

We demonstrate the presence of S100A8 and S100A9 proteins in the wall and thrombosed lumen of an enlarged intracranial aneurysm after flow diverter treatment. These proteins have shown to play an important role in vascular inflammation and may serve as a biomarker and potential therapeutic target for intracranial aneurysms.

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**KEYWORDS**
Intracranial aneurysm; flow diverter; aneurysm enlargement; S100A8; S100A9

## Case report

### History and clinical course

A 52-year-old woman presented with progressive retro-orbital pain and vomiting. Digital subtraction angiography (DSA) demonstrated a giant aneurysm originating from the left internal carotid artery (Figure 1(A)). Because of progressive symptomatology, the aneurysm was treated with a single flow diverter (FD) (Surpass Streamline, 4.0 × 30mm, Stryker Neurovascular, Fremont, California, United States). Before placement, the patient was given 500 mg acetylsalicylic acid intravenously. Acetylsalicylic acid (100 mg, lifelong) and clopidogrel (75 mg, 3 months) was continued daily after the procedure. The patient was discharged three days after treatment without residual neurological signs or symptoms.

After two weeks, the patient returned with retro-orbital headaches and slight worsening of vision in the left eye. Her vision further deteriorated in the following weeks (Online Supplement 1) and follow-up imaging was performed several times. Four weeks after treatment, magnetic resonance angiography (MRA) showed an almost completely thrombosed aneurysm with compression on the optic chiasm and no signs of recent ischemia. Six weeks after treatment, MRA and MRI with contrast showed no significant changes compared with the first MRA except diffusion restriction on diffusion-weighted imaging in the aneurysm lumen. DSA showed a completely occluded aneurysm and patency of all perforators, including the ophthalmic artery (Figure 1(B)).

Because the progressive vision loss did not respond to anti-inflammatory medication, we decided to decompress the optic chiasm by partial resection of the aneurysm. At surgery, compression of the optic chiasm and optic nerves was observed. The aneurysm was covered by vasa vasorum (Online Supplement 2). The superior part of the aneurysm was debulked and aneurysm tissue was collected from the wall and the intraluminal thrombus for histological examination. Vasa vasorum was coagulated to prevent bleeding. The patient recovered well and her visual fields and visual acuity was completely restored within 8 weeks after decompressive surgery (Online Supplement 1). Thrombus organization and aneurysm regression without diffusion restriction was seen on MRI 4 months after debulking. Patient consent regarding publication was obtained.

### Assessment of aneurysm volume

In order to assess aneurysm volume more precisely, subsequent imaging studies were segmented using Horos (The Horos Project, Version 2.0.0), Matlab (v.2016a) and 3ds Max (v.2016) (Figure 1(C)). The parent artery was excluded when calculating aneurysm volume. An increase in aneurysm volume was observed 8 hours after treatment (CT-perfusion, +1.18 $cm^3$ (18%)) and 6 weeks after treatment (MRI, +2.42 $cm^3$ (36%)). This resulted in compression of the optic chiasm and nerve. At 4 months' follow-up, the aneurysm had decreased in volume.

### Histology and immunohistochemistry

Collected tissues were fixed, embedded in paraffin and sectioned at 4 µm. Haematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) with custom-made anti-human S100A8 and S100A9 antibodies were performed.

H&E stained material showed a thrombus in different stages of organization. Some parts consisted of fresh, non-organized

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Supplemental data for this article can be accessed here.

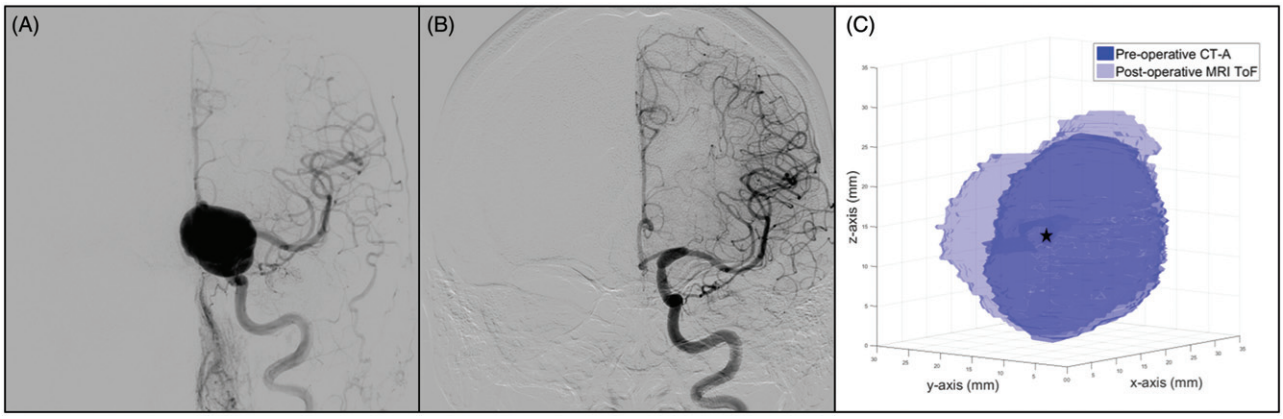


**Figure 1.** Cerebral DSA displaying a giant left ICA aneurysm before (A) and 7 weeks after (B) flow diverter treatment. 3D reconstructions of the aneurysms before and 6 weeks after flow-diverter placement (C). Axial view of pre-surgery (CT-A, dark) and 6 weeks post-surgery (MRI light). The ostium of the aneurysm is marked by a star.

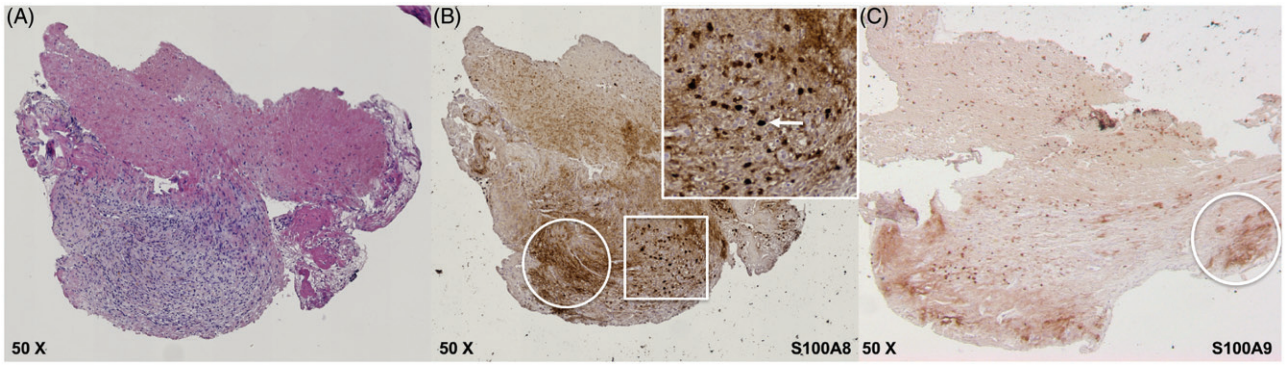


**Figure 2.** Histological studies (50X). Haematoxylin & Eosin staining (A): Partly fresh, partly organized thrombus. S100A8 (B) and S100A9 (C) immunohistochemistry. Focal spots of S100A8 S100A9 are seen in macrophages (Insert B, arrow) and a diffuse extracellular presence is seen around fibroblasts (circles).

thrombus, while other parts were more organized with fibroblast-filled tissue (Figure 2(A)). Macrophages and neutrophils were seen throughout the thrombus, both intact and partly degraded.

IHC showed that both S100A8 and S100A9 proteins were abundantly expressed in all samples (Figure 2(B,C)). Positive staining was not only seen within macrophages and neutrophils, but also in great amounts in the extracellular space. It was found around degrading myeloid cells and in high amounts around fibroblasts.

## Discussion

### *S100/calgranulins*

To our knowledge, this is the first report demonstrating the presence of S100A8 and S100A9 on IHC in an intracranial aneurysm.

Gene expression levels of S100A8 and S100A9 have recently been found upregulated in both ruptured and unruptured intracranial aneurysms, however no histological confirmation is reported.[1]

S100A8 and S100A9 expression can be induced upon activation in endothelial cells, vascular smooth muscle cells (VSMC) and fibroblasts. S100A8 and S100A9 expression amplifies the vascular inflammatory reaction by activating the vascular endothelium, inducing proliferation of VSMCs to the synthetic cell type and promoting further influx of leukocytes by the release of cytokines and chemokines.[2]

Previous reports have shown S100A8 and S100A9 to be an important moderator of vascular disease.[2] A 30% reduction in atherosclerotic lesions was observed in S100A8 and S100A9 depleted mice due to a reduction of macrophages at lesion sites. S100A8 and S100A9 depletion not only resulted in less atherosclerotic lesions but also in diminished neointimal thickening after injury and smaller lesion size after thrombo-haemorrhagic vasculitis.[3] Similarities between aneurysms and atherosclerosis make these findings interesting for the field of aneurysm research.

### *S100 & enlargement*

Flow diverter placement induces flow stagnation and rapid thrombus formation. In some patients, expression of pro-inflammatory cytokines in the freshly formed blood clot may induce and sustain the inflammatory state of the thrombus and prevent it from becoming stable. Vasa vasorum, seen during surgery in our case, may provide an alternative pathway for the influx of inflammatory cells as the aneurysm lumen is decoupled from the parent artery. This might explain why the aneurysm

volume kept increasing after FD placement and why the thrombus displayed such a heterogeneous image despite occlusion on DSA.

The observed aneurysm enlargement and the heterogeneous histological image might be related to of the presence of cytokines in general and more specifically of S100A8 and S100A9 Calgranulins that could prolong the inflammatory state of the thrombosed aneurysm.[3] Future research should investigate the role of S100A8 and S100A9 in aneurysm healing and rupture.

### *Clinical management*

Clinical deterioration after FD placement has been reported previously. Conservative management usually leads to spontaneous improvement, but in some cases FD placement leads to permanent deficits or, even worse, delayed ruptures. Currently, it is impossible to predict which aneurysms will progress beyond the point where it leads to irreversible clinical problems. The presented patient experienced severe and progressive visual deterioration, despite steroid treatment. In this case, we decided that surgical debulking was the best option to prevent permanent neurological damage.

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## Disclosure statement

Joost de Vries, MD PhD is a consultant for Stryker neurovascular. All other authors report no conflicts of interest.

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